PET Drug Inspection

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PET Drug Inspections During Fiscal year 2014/2015

Pre-approval and CGMP inspection status:

- All inspections were PAI+ CGMP inspections
- 94% of the pending PET facilities from ANDA backlog were inspected by Dec 2014
- 40 site inspections were completed in FY 2014
- 22 Site inspections have been completed so far for the FY2015 inspectional plan
- Follow-up inspections to post regulatory actions (e.g. untitled letter, regulatory meetings etc.) are on-going

"Current" in CGMP means...

Dynamic and evolves over time
Based on what?

Risk; cost/benefit; response to problems

Basic standards are currently being expected
which are both "feasible and valuable" in assuring safety and quality of PET Drugs

Balanced Approach
Minimum Standards Based On:

- Characteristics of PET drugs
  - See next slide
- Scale and scope of production across all PET drug production facilities
  - Commercial PET facility: 3 to 6 batches/day
  - Academic, hospital: 1 to 2 batches/day
- Risk assessment: no impact to drug quality and patients' safety

PET Drug Characteristics

- Short half life (2 min. to ~2 hours)
- Small batch size (30- 50 ml)
- Entire batch is contained in one vial. Test sample comes from product vial- Entire batch is tested
- Automated chemical synthesis
- In-process intermediates are not isolated and tested.
- Short production process (less than 2 hours).
- Multiple batches produced daily
- Few personnel (3-4 including Cyclotron operator)
- Small facility (typically 2-3 rooms for manufacturing and QC)

Laminar Flow Hood

- Qualification and requalification:
  - All hoods tested, qualified, cleaned, maintained, and re-qualified annually according to established SOP's
  - Qualification documented: particle counts, velocity, HEPA filter integrity, and smoke study
  - Smoke study: Acceptable to conduct dynamic only one time (initial) or upon major repair;
  - LAF should not be cluttered or used for storage
- Prior to processing: Disinfect LAF with sterile disinfectant and sterile wipes. Wipe down materials with sterile wipes
- Viable monitoring required: air and surface

Production Area

- Area may be classified, not a requirement but highly recommended
  - Corporate PET facilities: usually classified cleanroom environments
  - Academic & hospital: laboratory, not classified
- Must be clean and controlled (additional controls and cleaning/monitoring may be required if not classified)
- Well organized facility design and process flow to prevent contamination and cross contamination

Minimum Standards For Hot Cell

- Hot cells have HEPA filtration, but not a requirement; but should be at least clean and controlled for production
- Area disinfected (using sterile disinfectant and wipe) before production each day
- Verify suitability of the environment each production day by viable monitoring* (air, surface, personnel)

  ** monitoring at least once a day or worst case*
- Smoke study not required: hot cell is negatively pressurized

Media Fill Requirements

- Ensure that media fills simulate production process as closely as possible, including the pre-assembly of product vial in LAF, sterile filtration/ dilution/ withdrawal of QC samples in the hot cell/LAF
- Media fills must include positive control to demonstrate media used supports growth
- Media fills should be conducted in the same area (LAF, hot cell) where production occurs
- Each operator should be qualified by 3 successful media fill runs and re-qualified by one run annually

EM: Minimum Expectations

- Viable monitoring should be conducted *at least once* on each production day
  - Air (active air or settle plate) in LAF and hot cell during operation or at the end (or justified worst case)
  - Personnel monitoring: fingertips
  - Surface (work surface) at the end of operation
    - LAF: same day
    - Hot cell: normally next day (radiation concern)
- 2nd person verification for viable monitoring results not required

Incubators

- Temperature mapping of incubator not required- small lab incubator
- Daily temperature recording of the incubators
- Each growth media should be incubated in appropriate temperature incubators
  - Incubation of Tryptic Soya Broth at room temperature (instead of 20-25 degree incubator) not acceptable

Data Integrity Issues

- Not recording activities contemporaneously
- Backdating batch record entries
- Unsupportable data entries- Lacking raw data
- Copying existing data as new data
- Re-running analytical samples without justification
- Discarding raw data

Case 1: Manufacturing Site

Background:

- Application with sponsor site being the only manufacturer of the final drug product
- FDA inspection revealed major quality system deficiencies and the application was withheld. The firm submitted the corrective action plan which was acceptable.

What Happened Next:

- FDA visited the site for a follow up inspection after 1.5 years
- FDA found the firm stopped manufacturing
- Final finished drug was procured from another PET manufacturer
- The firm failed to notify FDA regarding the change regarding facility closure and procurement of PET drug
- Regulatory meeting was held to discuss the observations

Case 1:Manufacturing Site

Option 1

- Formally withdraw the site from the application
- Submit an addendum to the application with the new contract sites

Option 2

- Start up operation at the original site and
- Repeat all validation/qualification activities
- Notify FDA regarding the readiness for inspection

Outcome

- Firm decided to go with option 2
- Application will not be approved until site is found acceptable after a follow up FDA inspection

Case 2 :Final Product Release

Background:

- The firm delivers bulk final drug product to hospital pharmacy immediately after manufacturing as a standard practice
- The product is transferred by a private van which belongs to the firm. The product is handed over to the hospital.
- The firm performs the QC tests after the product leaves the facility. Product release is communicated over the phone to the hospital

Case 2 :Final Product Release

What happens next:

- Firm SOP states that final QC tests and release is completed before product is shipped to the Pharmacy.
- The GC equipment fails the suitability test. A malfunction is identified . No GC test conducted for the sample.
- The firm completes rest of the QC tests and relays the product release over the phone to the pharmacy without a conditional release process completed for the product
- QC test results are documented and completed the next day after the patient dose is administered
- This practice was a standard practice at the site

Questions?

For More CGMP Information…

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PET Drug Web page

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm